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NEWS 12	Nov 29	DWPI revisions to NTIS and US Provisional Numbers
NEWS 13	Nov 30	Files VETU and VETB to have open access
NEWS 14	Dec 10	WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
NEWS 15	Dec 10	DGENE BLAST Homology Search
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NEWS 17	Dec 17	STANDARDS now available on STN
NEWS 18	Dec 17	New fields for DPCI
NEWS 19	Dec 19	CAS Roles modified
NEWS 20	Dec 19	1907-1946 data and page images added to CA and CAplus
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FILE 'SCISEARCH' ENTERED AT 09:42:47 ON 12 FEB 2002

FILE 'CAPLUS' ENTERED AT 09:42:47 ON 12 FEB 2002


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=> s T cell tolerance
   3 FILES SEARCHED...
L1         3250 T CELL TOLERANCE

=> s l1 and graft rejection
L2          105 L1 AND GRAFT REJECTION

=> s l2 and TGF beta
   3 FILES SEARCHED...
L3            2 L2 AND TGF BETA

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L4             1 DUP REMOVE L3 (1 DUPLICATE REMOVED)

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L4 ANSWER 1 OF 1 MEDLINE DUPLICATE 1

2001043452 Document Number: 20484122. PubMed ID: 11027453. Enhanced immunological tolerance against allograft rejection by oral administration of allogeneic antigen linked to cholera toxin B subunit. Sun J B; Li B L; Czerkinsky C; Holmgren J. (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, S-413 46, Sweden.. Jia-Bin.Sun@microbio.gu.se) . CLINICAL IMMUNOLOGY, (2000 Nov) 97 (2) 130-9. Journal code: C90. ISSN: 1521-6616. Pub. country: United States. Language: English.

AB A single oral intragastric administration of cholera toxin B subunit (CTB) conjugated to allogeneic thymocytes (ATC, 4 x 10(7) cells) under conditions allowing the CTB to bind the complex to GM1 ganglioside receptors was shown to be efficacious in inducing peripheral **T cell tolerance** associated with significant suppression of both primary and secondary accelerated rejection of heart allografts when tested in mice. Allogeneic in vivo delayed-type hypersensitivity (DTH), in vitro cytotoxicity responses, and mixed lymphocyte reactions (MLR) by T cells from mesenteric lymph nodes (MLN), popliteal lymph nodes (PLN), and spleen were significantly reduced in mice treated with the CTB-ATC conjugate, as were also the numbers of cells in these organs producing IL-2, IFN-gamma, or IL-4. In contrast, a marked increase in the production of IL-4 in Peyer's patches (PP) and of **TGF-beta**(1) in PLN was observed. The suppressive potential of T cells from PP and/or MLN after oral treatment with CTB-ATC was further evident by intraperitoneal transfer of such cells from CTB-ATC-treated animals to primed recipients, which led to marked suppression of both allogen-specific DTH and MLR responses. A critical role for PP in inducing

peripheral tolerance after oral CTB-ATC treatment was indicated by the absence of tolerance induction in animals whose PP had been destroyed before treatment with CTB-ATC. The results indicate that the protection against allograft rejection by oral treatment with CTB-ATC is mediated by T cells and associated with a strong induction of IL-4 production at mucosal sites and **TGF-beta**(1) at the effector sites.


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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:42:47 ON
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L1          3250 S T CELL TOLERANCE
L2           105 S L1 AND GRAFT REJECTION
L3             2 S L2 AND TGF BETA
L4             1 DUP REMOVE L3 (1 DUPLICATE REMOVED)

=> s l1 and ex vivo
L5            23 L1 AND EX VIVO

=> s l5 and interleukin 2 or 5
L6     11222831 L5 AND INTERLEUKIN 2 OR 5

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PROCESSING COMPLETED FOR L5
L7             11 DUP REMOVE L5 (12 DUPLICATES REMOVED)

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L7   ANSWER 7 OF 11      MEDLINE                                  DUPLICATE 3
1998391026  Document Number: 98391026.     PubMed ID: 9725210.
     Tumor-infiltrating lymphocytes exhibiting high ex vivo
     cytolytic activity fail to prevent murine melanoma tumor growth in vivo.
     Prevost-Blondel A; Zimmermann C; Stemmer C; Kulmburg P; Rosenthal F M;
     Pircher H. (Department of Immunology, Institute of Medical Microbiology
     and Hygiene, University of Freiburg, Germany. ) JOURNAL OF IMMUNOLOGY,
     (1998 Sep 1) 161 (5) 2187-94.  Journal code: IFB; 2985117R. ISSN:
     0022-1767. Pub. country: United States. Language: English.
AB   The identification of tumor-associated Ags recognized by CD8+ CTL and
     prevention of tumor outgrowth by adoptive transfer of these CTL
     demonstrates that CD8+ T cells play a major role in antitumor immunity. We
     have generated B16.F10 melanoma cells that express the glycoprotein
     epitope amino acid 33-41 (GP33) of the lymphocytic choriomeningitis virus
     (LCMV) to examine antitumor CD8+ T cell response in C57BL/6 mice immune to
     LCMV and in mice transgenic for the LCMV GP33-specific P14 TCR (P14 TCR
     mice). We find that B16.F10GP33 tumor cells grew in syngeneic C57BL/6 mice
     without inducing T cell tolerance. LCMV
     infection or adoptive transfer of LCMV-specific effector T cells delayed
     but did not prevent growth of preestablished tumors in these mice.
     However, B16.F10GP33 tumor cells were rejected in mice immune to LCMV and
     in mice treated with LCMV-specific effector T cells on the same day as the
     tumor. Surprisingly, B16.F10GP33 tumor cells grew in P14 TCR transgenic
     mice despite an abundance of tumor-associated Ag-specific CD8+ T cells. In
     these mice, freshly isolated tumor-infiltrating lymphocytes exhibited an
     activated phenotype and displayed high GP33-specific cytolytic activity
     when assessed ex vivo. Thus, B16.F10GP33 melanoma
     cells are able to initiate, but not to sustain, a GP33-specific CTL
     response sufficient to clear the tumor enduringly.

L7   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2002 ACS
2001:168120   Document No. 134:206587  Use of cytokines, cells, and mitogens to
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inhibit graft versus host disease. Horwitz, David A. (University of Southern California, USA). PCT Int. Appl. WO 2001016296 A2 20010308, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US40803 20000901. PRIORITY: US 1999-PV151987 19990901.

AB The field of the invention is generally related to pharmaceutical agents useful in treating graft-vs.-host disease in patients that have received allogenic bone marrow transplants. The invention provides methods for inducing **T cell tolerance** in a sample of **ex vivo** peripheral blood mononuclear cells comprising adding a suppressive-inducing compn. to the cells. The suppressive-inducing compn. can be interleukin-2, interleukin-10, transforming growth factor-.beta., or a mixt. The method also relates to a method whereby donor peripheral blood mononuclear cells are treated with a suppressive-inducing compn. to induce **T-cell tolerance**. The treated cells are then introduced into a recipient patient. T-cells can also be treated with transforming growth factor-.beta. and activated to become suppressor T-cells that inhibit graft vs. host disease.

L7 ANSWER 2 OF 11 MEDLINE DUPLICATE 1

2001361978 Document Number: 21315635. PubMed ID: 11423475. Indirect allorecognition in acquired thymic tolerance: induction of donor-specific permanent acceptance of rat islets by adoptive transfer of allopeptide-pulsed host myeloid and thymic dendritic cells. Oluwole O O; Depaz H A; Gopinathan R; Ali A; Garrovillo M; Jin M X; Hardy M A; Oluwole S F. (Department of Surgery, Columbia University College of Physicians and Surgeons, 630 W. 168th Street, New York, NY 10032, USA.) DIABETES, (2001 Jul) 50 (7) 1546-52. Journal code: E8X; 0372763. ISSN: 0012-1797. Pub. country: United States. Language: English.

AB Pancreatic islet transplantation remains a promising approach to the treatment of type 1 diabetes. Unfortunately, graft failure continues to occur because of immunologic rejection, despite the use of potent immunosuppressive agents. It is therefore reasoned that induction of peripheral tolerance by the use of self-dendritic cells (DCs) as a vehicle to deliver specific target antigens to self-T-cells without **ex vivo** manipulation of the recipient is an attractive strategy in the treatment of type 1 diabetes. The finding that intrathymic inoculation of an immunodominant WF major histocompatibility complex (MHC) Class I (RT1.A(u)) peptide five (P5) or P5-pulsed host myeloid DCs induces acquired thymic tolerance raises the possibility that adoptive transfer of allopeptide-primed host myeloid or lymphoid DCs might induce transplant tolerance. To address this hypothesis, we studied the effects of intravenous transfer of in vitro P5-pulsed syngeneic myeloid DCs or in vivo P5-primed syngeneic lymphoid (thymic) DCs on islet survival in the WF-to-ACI rat combination. In vivo primed thymic DCs isolated from ACI rats given intrathymic inoculation of P5 for 2 days were capable of in vitro restimulation of in vivo P5-primed T-cells (memory cells). In the first series of studies, we showed that intravenous-like intrathymic-inoculation of in vitro P5-pulsed host myeloid DCs induced donor-specific permanent acceptance of islets in recipients transiently immunosuppressed with antilymphocyte serum (ALS). We next examined whether thymic DCs isolated from animals that had been previously intrathymically inoculated with P5 could induce **T-cell tolerance**. The results showed that intravenous adoptive transfer of in vivo P5-primed thymic DCs led to donor-specific permanent acceptance of islets in recipients transiently immunosuppressed with ALS. This finding suggested that the thymic DCs take up and present P5 to developing

T-cells to induce **T-cell tolerance**, thus providing evidence of a direct link between indirect allorecognition and acquired thymic tolerance. The second series of studies examined the mechanisms involved in this model by exploring whether in vivo generation of peptide-specific alloreactive peripheral T-cells by intravenous inoculation of P5-pulsed self-DCs was responsible for the induction of **T-cell tolerance**. Intrathymic inoculation of splenic T-cells obtained from syngeneic ACI rats primed with intravenous injection of P5-pulsed DCs with a high in vitro proliferative response to P5 in the context of self-MHC induced donor-specific permanent acceptance of islets from WF donors. In addition, the clinically relevant model of intravenous injection of P5-activated T-cells combined with transient ALS immunosuppression similarly induced transplant tolerance, which was then abrogated by thymectomy of the recipient before intravenous injection of the activated T-cells. These data raise the possibility that circulation of peptide-activated T-cells to the host thymus plays a role in the induction and possibly the maintenance of **T-cell tolerance** in this model. Our findings suggest that intravenous administration of genetically engineered host DCs expressing alloMHC peptides might have therapeutic potential in clinical islet transplantation for the treatment of autoimmune diabetes.

L7 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2002 ACS

2001:418188 Document No. 135:179351 CD4+CD25+ immune regulatory cells are required for induction of tolerance to alloantigen via costimulatory blockade. Taylor, Patricia A.; Noelle, Randolph J.; Blazar, Bruce R. (Division of Bone Marrow Transplantation, University of Minnesota Cancer Center and Department of Pediatrics, Minneapolis, MN, 55455, USA). J. Exp. Med., 193(11), 1311-1317 (English) 2001. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB Immune regulatory CD4+CD25+ cells play a vital role in the induction and maintenance of self-tolerance and are essential for T cell homeostasis and the prevention of autoimmunity. Induction of tolerance to allogeneic donor grafts is a clin. desirable goal in bone marrow and solid organ transplantation. To det. whether CD4+CD25+ cells regulate T cell responses to alloantigen and are crit. for tolerance induction, murine CD4+ T cells were tolerized to alloantigen via **ex vivo** CD40 ligand (CD40L)/CD40 or CD28/cytotoxic T lymphocyte-assocd. antigen 4/B7 blockade resulting in secondary mixed leukocyte reaction hyporesponsiveness and tolerance to alloantigen in vivo. CD4+CD25+ T cells were potent regulators of alloresponses. Depletion of CD4+CD25+ T cells from the CD4+ responder population completely abrogated **ex vivo** tolerance induction to alloantigen as measured by intact responses to alloantigen restimulation in vitro and in vivo. Add back of CD4+CD25+ T cells to CD4+CD25 cultures restored tolerance induction. These data are the first to indicate that CD4+CD25+ cells are essential for the induction of tolerance to alloantigen and have important implications for tolerance-inducing strategies targeted at T cell costimulatory pathways.

L7 ANSWER 4 OF 11 MEDLINE DUPLICATE 2

2001076797 Document Number: 20540057. PubMed ID: 11086037.

Superantigen-induced CD4 **T cell tolerance** mediated by myeloid cells and IFN-gamma. Cauley L S; Miller E E; Yen M; Swain S L. (Trudeau Institute, Saranac Lake, NY 12983, USA.) JOURNAL OF IMMUNOLOGY, (2000 Dec 1) 165 (11) 6056-66. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have previously shown that systemic staphylococcal enterotoxin A (SEA) injections cause CD4 T cells in TCR-transgenic mice to become tolerant to subsequent **ex vivo** restimulation. An active IFN-gamma-dependent mechanism of suppression was responsible for the apparent unresponsiveness of the CD4 T cells. In this study, we analyze the response of CD4 T cells isolated throughout the first 10 days of the in vivo response to injected SEA. We show that CD4 T cells isolated at the

peak of the in vivo response undergo very little activation-induced cell death after sterile FACS sorting or restimulation in the presence of neutralizing Abs to IFN-gamma. We also show that the IFN-gamma-dependent tolerance develops soon after SEA injection in the spleens of both normal and TCR-transgenic mice. This suppression is dependent upon myeloid cells from the SEA-treated mice and is optimal when inducible NO synthase activity and reactive oxygen intermediates are both present. The data indicate that IFN-gamma, myeloid cells, and a combination of NO and reactive oxygen intermediates all contribute to a common pathway of T cell death that targets activated or responding CD4 T cells. Sorted Gr-1(+) cells from SEA-treated mice also directly suppress the response of naive CD4 T cells in mixed cultures, indicating that this tolerance mechanism may play a role in down-regulating other vigorous immune responses.

L7 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2002 ACS
1999:626069 Document No. 131:256340 Use of cytokines and mitogens to inhibit graft versus host disease. Horwitz, David A. (University of Southern California, USA). PCT Int. Appl. WO 9948524 A1 19990930, 37 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US4630 19990303. PRIORITY: US 1998-PV76677 19980303.

AB Disclosed is a method for inducing **T cell tolerance** in a sample of **ex vivo** peripheral blood mononuclear cells, comprising the addn. to said cells of immunosuppressive agents such as IL-10 and TGF-.beta.. Also described is a kit for carrying out such a method and the relevance of the latter for instance for suppressing Graft Vs. Host Disease in patients that have received allogenic bone marrow transplants.

L7 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2002 ACS
1999:628071 Document No. 131:321311 Induction of CD4+ T cell alloantigen-specific hyporesponsiveness by IL-10 and TGF-.beta.. Zeller, Jay C.; Panoskaltsis-Mortari, Angela; Murphy, William J.; Ruscetti, Francis W.; Narula, Satwant; Roncarolo, Maria G.; Blazar, Bruce R. (Department of Pediatrics, Division of Bone Marrow Transplantation, University of Minnesota Cancer Center, Minneapolis, MN, 55455, USA). J. Immunol., 163(7), 3684-3691 (English) 1999. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB Induction and maintenance of Ag-specific tolerance are pivotal for immune homeostasis, prevention of autoimmune disorders, and the goal of transplantation. Recent studies suggest that certain cytokines, notably IL-10 and TGF-.beta., may play a role in down-regulating immune functions. To further examine the role of cytokines in Ag-specific hyporesponsiveness, murine CD4+ T cells were exposed **ex vivo** to alloantigen-bearing stimulators in the presence of exogenous IL-10 and/or TGF-.beta.. Primary but not secondary alloantigen proliferative responses were inhibited by IL-10 alone. However, the combined addn. of IL-10 + TGF-.beta. markedly induced alloantigen hyporesponsiveness in both primary and secondary MLR cultures. Alloantigen-specific hyporesponsiveness was obsd. also under conditions in which nominal Ag responses were intact. In adoptive transfer expts., IL-10 + TGF-.beta.-treated CD4+ T cells, but not T cells treated with either cytokine alone, were markedly impaired in inducing graft-vs-host disease alloresponses to MHC class II disparate recipients. These data provide the first formal evidence that IL-10 and TGF-.beta. have at least an additive effect in inducing alloantigen-specific tolerance, and that in vitro cytokines can be exploited to suppress CD4+ T cell-mediated Ag-specific responses in vivo.

L7 ANSWER 7 OF 11 MEDLINE DUPLICATE 3
1998391026 Document Number: 98391026. PubMed ID: 9725210.
Tumor-infiltrating lymphocytes exhibiting high **ex vivo** cytolytic activity fail to prevent murine melanoma tumor growth in vivo.
Prevost-Blondel A; Zimmermann C; Stemmer C; Kulmburg P; Rosenthal F M; Pircher H. (Department of Immunology, Institute of Medical Microbiology and Hygiene, University of Freiburg, Germany.) JOURNAL OF IMMUNOLOGY, (1998 Sep 1) 161 (5) 2187-94. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The identification of tumor-associated Ags recognized by CD8+ CTL and prevention of tumor outgrowth by adoptive transfer of these CTL demonstrates that CD8+ T cells play a major role in antitumor immunity. We have generated B16.F10 melanoma cells that express the glycoprotein epitope amino acid 33-41 (GP33) of the lymphocytic choriomeningitis virus (LCMV) to examine antitumor CD8+ T cell response in C57BL/6 mice immune to LCMV and in mice transgenic for the LCMV GP33-specific P14 TCR (P14 TCR mice). We find that B16.F10GP33 tumor cells grew in syngeneic C57BL/6 mice without inducing **T cell tolerance**. LCMV infection or adoptive transfer of LCMV-specific effector T cells delayed but did not prevent growth of preestablished tumors in these mice. However, B16.F10GP33 tumor cells were rejected in mice immune to LCMV and in mice treated with LCMV-specific effector T cells on the same day as the tumor. Surprisingly, B16.F10GP33 tumor cells grew in P14 TCR transgenic mice despite an abundance of tumor-associated Ag-specific CD8+ T cells. In these mice, freshly isolated tumor-infiltrating lymphocytes exhibited an activated phenotype and displayed high GP33-specific cytolytic activity when assessed **ex vivo**. Thus, B16.F10GP33 melanoma cells are able to initiate, but not to sustain, a GP33-specific CTL response sufficient to clear the tumor enduringly.

L7 ANSWER 8 OF 11 MEDLINE DUPLICATE 4
1998224474 Document Number: 98224474. PubMed ID: 9564804. Effects of peptide therapy on **ex vivo** T-cell responses. Marcotte
G V; Braun C M; Norman P S; Nicodemus C F; Kagey-Sobotka A; Lichtenstein L M; Essayan D M. (Division of Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998 Apr) 101 (4 Pt 1) 506-13. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Peptide therapy targets T cells directly with short peptides containing multiple T-cell receptor epitopes. Murine studies suggest T-cell anergy as the mechanism of action; however, changes in T-cell cytokine profiles may be more relevant in human beings. OBJECTIVE: We sought to study the effects of peptide therapy on **ex vivo** antigen-specific T-cell responses. METHODS: Antigen-specific T-cell lines were generated from subjects enrolled in a double-blind, placebo controlled, two-dose study of the ALLERVAX CAT therapeutic, containing Fel d 1 peptides (ImmuLogic Pharmaceutical Corp., Waltham, Mass.) (n = 7, 8, and 7, respectively, for groups receiving placebo, 75 microg, or 750 microg). Each subject had three lines propagated before and after receiving peptide therapy; antigens used were cat hair extract, Fel d 1 peptides, and tetanus toxoid (negative control). Proliferative responses and cytokine generation from each line were assessed after two restimulations with antigen and autologous antigen-presenting cells. RESULTS: The Fel d 1 peptide lines showed a dose-dependent decrease of IL-4 production (p = 0.02 and 0.025, respectively, for the 750 microg group vs both the 75 microg and placebo groups). IL-4 production from the cat hair allergen extract lines and interferon-gamma production from both the Fel d 1 peptide lines and cat hair allergen extract lines showed no statistically significant changes. The control tetanus toxoid lines showed no changes in cytokine production; there were no significant changes in proliferation with any of the antigens in any of the treatment groups. In the clinical arm of the trial, only the 750 microg dose of peptides produced a significant response. CONCLUSIONS: Peptide therapy induces a significant, dose-dependent decrease in peptide-stimulated IL-4

production, consistent with either a shift in T-cell phenotype or peptide-specific **T-cell tolerance**.

L7 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:257468 Document No.: PREV199800257468. Effects of peptide therapy on **ex vivo** T-cell responses. Marcotte, Gregory V.; Braun, Christine M.; Norman, Philip S.; Nicodemus, Christopher E.; Kagey-Sobotka, Anne; Lichtenstein, Lawrence M.; Essayan, David M. (1). (1) Johns Hopkins Asthma Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224 USA. Journal of Allergy and Clinical Immunology, (April, 1998) Vol. 10, No. 4 PART 1, pp. 506-513. ISSN: 0091-6749. Language: English.

AB Background: Peptide therapy targets T cells directly with short peptides containing multiple T-cell receptor epitopes. Murine studies suggest T-cell anergy as the mechanism of action; however, changes in T-cell cytokine profiles may be more relevant in human beings. Objective: We sought to study the effects of peptide therapy on **ex vivo** antigen-specific T-cell responses. Methods: Antigen-specific T-cell lines were generated from subjects enrolled in a double-blind, placebo controlled, two-dose study of the ALLERVAX CAT therapeutic, containing Fel d 1 peptides (ImmuLogic Pharmaceutical Corp., Waltham, Mass.) (n=7, 8, and 7, respectively, for groups receiving placebo, 75 mug, or 750 mug). Each subject had three lines propagated before and after receiving peptide therapy; antigens used were cat hair extract, Fel d 1 peptides, and tetanus toxoid (negative control). Proliferative responses and cytokine generation from each line were assessed after two restimulations with antigen and autologous antigen-presenting cells. Results: The Fel d 1 peptide lines showed a dose-dependent decrease of IL-4 production (p=0.02 and 0.025, respectively, for the 750 Kg group vs both the 75 mug and placebo groups). IL-4 production from the cat hair allergen extract lines and interferon-gamma production from both the Fel d 1 peptide lines and cat hair allergen extract lines showed no statistically significant changes. The control tetanus toxoid lines showed no changes in cytokine production; there were no significant changes in proliferation with any of the antigens in any of the treatment groups. In the clinical arm of the trial, only the 750 mug dose of peptides produced a significant response. Conclusions: Peptide therapy induces a significant, dose-dependent decrease in peptide-stimulated IL-4 production, consistent with either a shift in T-cell phenotype or peptide-specific **T-cell tolerance**.

L7 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 2002 ISI (R)
96:620928 The Genuine Article (R) Number: VC450. THYMIC DEPENDENCE OF LOSS OF TOLERANCE IN MIXED ALLOGENEIC BONE-MARROW CHIMERAS AFTER DEPLETION OF DONOR ANTIGEN - PERIPHERAL MECHANISMS DO NOT CONTRIBUTE TO MAINTENANCE OF TOLERANCE. KHAN A; TOMITA Y; SYKES M (Reprint). HARVARD UNIV, MASSACHUSETTS GEN HOSP, TRANSPLANTAT BIOL RES CTR, SURG SERV, SCH MED, MGH-E, BOSTON, MA, 02129 (Reprint); HARVARD UNIV, MASSACHUSETTS GEN HOSP, TRANSPLANTAT BIOL RES CTR, SURG SERV, SCH MED, BOSTON, MA, 02129. TRANSPLANTATION (15 AUG 1996) Vol. 62, No. 3, pp. 380-387. ISSN: 0041-1337 . Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A nonmyeloablative conditioning regimen has recently been developed that allows allogeneic marrow engraftment with induction of permanent mixed chimerism and donor-specific tolerance across fully MHC-mismatched, allogeneic barriers, We recently demonstrated that tolerance can be broken in these chimeras by administration of an anti-donar class I-specific monoelonal antibody that eliminates donor hematopoietic cells, We have now investigated the role of the thymus ill the loss of tolerance observed when chimerism is eliminated in this manner, Mixed chimeras were prepared in B10 (H2(b)) recipients by treatment with depleting anti-CD4 and anti-CDS mAbs, 3-Gy whole body irradiation, and 7-Gy thymic irradiation, followed by B10.A (H2(a)) bone marrow transplantation. Chimeras were thymectomized 7 weeks later, and were either untreated or were depleted of donor cells with anti-donor class I (D-d-specific) mAb 34-2-12. Control

chimeras that were not thymectomized also received anti-donor monoclonal antibodies or no further treatment, Of the four groups, only euthymic animals that were depleted of donor antigen showed a loss of tolerance, as evidenced by rejection of B10.A skin grafts. In contrast to untreated central and thymectomized, anti-Dd-treated chimeras, these euthymic anti-Dd-treated chimeras showed significant recovery of V beta 11(+) T cells, which can recognize Mtv antigens presented by donor I-E molecules, The requirement for a thymus for lass of tolerance in the absence of donor antigen was verified in an adoptive transfer model, in which chimera (B10.A-->B10) spleen cells were depleted of donor-type cells **ex vivo**, adoptively transferred into B6 nu/nu mice, and then further depleted of donor-type antigen with monoclonal antibody treatment in vivo. These B6 nu/nu mice maintained donor-specific tolerance to B10.A skin grafts. The absence of active suppression as a potent mechanism of tolerance in long-term mixed chimeras was confirmed by the loss of mixed chimerism and of tolerance that was readily induced by injection of naive host-type spleen cells. Together, our results suggest that in mixed allogeneic chimeras, intrathymic clonal deletion, and not peripheral suppression or anergy, is the major mechanism maintaining donor-specific tolerance.

L7 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1995:384152 Document No.: PREV199598398452. Induction of anergy in **ex vivo** alloreactive CD4 T cells by activated T cell expressing MHC class II. Satyaraj, E.; Rath, S.; Bal, V.. National Inst. Immunology, New Delhi 110 067 India. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 599. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

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(FILE 'HOME' ENTERED AT 09:42:24 ON 12 FEB 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:42:47 ON 12 FEB 2002

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L1          3250 S T CELL TOLERANCE
L2           105 S L1 AND GRAFT REJECTION
L3             2 S L2 AND TGF BETA
L4             1 DUP REMOVE L3 (1 DUPLICATE REMOVED)
L5            23 S L1 AND EX VIVO
L6      11222831 S L5 AND INTERLEUKIN 2 OR 5
L7            11 DUP REMOVE L5 (12 DUPLICATES REMOVED)

=> s l2 and ex vivo
L8             0 L2 AND EX VIVO

=> s l1 and induction
L9          1521 L1 AND INDUCTION

=> s l9 and ex vivo
L10            8 L9 AND EX VIVO

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11            5 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> d l11 1-5 cbib abs

L11 ANSWER 1 OF 5      MEDLINE                              DUPLICATE 1
2001361978 Document Number: 21315635.    PubMed ID: 11423475.    Indirect
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allorecognition in acquired thymic tolerance: **induction** of donor-specific permanent acceptance of rat islets by adoptive transfer of allopeptide-pulsed host myeloid and thymic dendritic cells. Oluwole O O; Depaz H A; Gopinathan R; Ali A; Garrovillo M; Jin M X; Hardy M A; Oluwole S F. (Department of Surgery, Columbia University College of Physicians and Surgeons, 630 W. 168th Street, New York, NY 10032, USA.) DIABETES, (2001 Jul) 50 (7) 1546-52. Journal code: E8X; 0372763. ISSN: 0012-1797. Pub. country: United States. Language: English.

AB Pancreatic islet transplantation remains a promising approach to the treatment of type 1 diabetes. Unfortunately, graft failure continues to occur because of immunologic rejection, despite the use of potent immunosuppressive agents. It is therefore reasoned that **induction** of peripheral tolerance by the use of self-dendritic cells (DCs) as a vehicle to deliver specific target antigens to self-T-cells without **ex vivo** manipulation of the recipient is an attractive strategy in the treatment of type 1 diabetes. The finding that intrathymic inoculation of an immunodominant WF major histocompatibility complex (MHC) Class I (RT1.A(u)) peptide five (P5) or P5-pulsed host myeloid DCs induces acquired thymic tolerance raises the possibility that adoptive transfer of allopeptide-primed host myeloid or lymphoid DCs might induce transplant tolerance. To address this hypothesis, we studied the effects of intravenous transfer of in vitro P5-pulsed syngeneic myeloid DCs or in vivo P5-primed syngeneic lymphoid (thymic) DCs on islet survival in the WF-to-ACI rat combination. In vivo primed thymic DCs isolated from ACI rats given intrathymic inoculation of P5 for 2 days were capable of in vitro restimulation of in vivo P5-primed T-cells (memory cells). In the first series of studies, we showed that intravenous-like intrathymic-inoculation of in vitro P5-pulsed host myeloid DCs induced donor-specific permanent acceptance of islets in recipients transiently immunosuppressed with antilymphocyte serum (ALS). We next examined whether thymic DCs isolated from animals that had been previously intrathymically inoculated with P5 could induce **T-cell tolerance**. The results showed that intravenous adoptive transfer of in vivo P5-primed thymic DCs led to donor-specific permanent acceptance of islets in recipients transiently immunosuppressed with ALS. This finding suggested that the thymic DCs take up and present P5 to developing T-cells to induce **T-cell tolerance**, thus providing evidence of a direct link between indirect allorecognition and acquired thymic tolerance. The second series of studies examined the mechanisms involved in this model by exploring whether in vivo generation of peptide-specific alloreactive peripheral T-cells by intravenous inoculation of P5-pulsed self-DCs was responsible for the **induction** of **T-cell tolerance**.
Intrathymic inoculation of splenic T-cells obtained from syngeneic ACI rats primed with intravenous injection of P5-pulsed DCs with a high in vitro proliferative response to P5 in the context of self-MHC induced donor-specific permanent acceptance of islets from WF donors. In addition, the clinically relevant model of intravenous injection of P5-activated T-cells combined with transient ALS immunosuppression similarly induced transplant tolerance, which was then abrogated by thymectomy of the recipient before intravenous injection of the activated T-cells. These data raise the possibility that circulation of peptide-activated T-cells to the host thymus plays a role in the **induction** and possibly the maintenance of **T-cell tolerance** in this model. Our findings suggest that intravenous administration of genetically engineered host DCs expressing alloMHC peptides might have therapeutic potential in clinical islet transplantation for the treatment of autoimmune diabetes.

L11 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:418188 Document No. 135:179351 CD4+CD25+ immune regulatory cells are required for **induction** of tolerance to alloantigen via costimulatory blockade. Taylor, Patricia A.; Noelle, Randolph J.; Blazar, Bruce R. (Division of Bone Marrow Transplantation, University of Minnesota

Cancer Center and Department of Pediatrics, Minneapolis, MN, 55455, USA). J. Exp. Med., 193(11), 1311-1317 (English) 2001. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB Immune regulatory CD4+CD25+ cells play a vital role in the **induction** and maintenance of self-tolerance and are essential for T cell homeostasis and the prevention of autoimmunity. **Induction** of tolerance to allogeneic donor grafts is a clin. desirable goal in bone marrow and solid organ transplantation. To det. whether CD4+CD25+ cells regulate T cell responses to alloantigen and are crit. for tolerance **induction**, murine CD4+ T cells were tolerized to alloantigen via **ex vivo** CD40 ligand (CD40L)/CD40 or CD28/cytotoxic T lymphocyte-assocd. antigen 4/B7 blockade resulting in secondary mixed leukocyte reaction hyporesponsiveness and tolerance to alloantigen in vivo. CD4+CD25+ T cells were potent regulators of alloresponses. Depletion of CD4+CD25+ T cells from the CD4+ responder population completely abrogated **ex vivo** tolerance **induction** to alloantigen as measured by intact responses to alloantigen restimulation in vitro and in vivo. Add back of CD4+CD25+ T cells to CD4+CD25 cultures restored tolerance **induction**. These data are the first to indicate that CD4+CD25+ cells are essential for the **induction** of tolerance to alloantigen and have important implications for tolerance-inducing strategies targeted at T cell costimulatory pathways.

L11 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS

1999:628071 Document No. 131:321311 **Induction** of CD4+ T cell alloantigen-specific hyporesponsiveness by IL-10 and TGF-.beta.. Zeller, Jay C.; Panoskaltsis-Mortari, Angela; Murphy, William J.; Ruscetti, Francis W.; Narula, Satwant; Roncarolo, Maria G.; Blazar, Bruce R. (Department of Pediatrics, Division of Bone Marrow Transplantation, University of Minnesota Cancer Center, Minneapolis, MN, 55455, USA). J. Immunol., 163(7), 3684-3691 (English) 1999. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB **Induction** and maintenance of Ag-specific tolerance are pivotal for immune homeostasis, prevention of autoimmune disorders, and the goal of transplantation. Recent studies suggest that certain cytokines, notably IL-10 and TGF-.beta., may play a role in down-regulating immune functions. To further examine the role of cytokines in Ag-specific hyporesponsiveness, murine CD4+ T cells were exposed **ex vivo** to alloantigen-bearing stimulators in the presence of exogenous IL-10 and/or TGF-.beta.. Primary but not secondary alloantigen proliferative responses were inhibited by IL-10 alone. However, the combined addn. of IL-10 + TGF-.beta. markedly induced alloantigen hyporesponsiveness in both primary and secondary MLR cultures. Alloantigen-specific hyporesponsiveness was obsd. also under conditions in which nominal Ag responses were intact. In adoptive transfer expts., IL-10 + TGF-.beta.-treated CD4+ T cells, but not T cells treated with either cytokine alone, were markedly impaired in inducing graft-vs-host disease alloresponses to MHC class II disparate recipients. These data provide the first formal evidence that IL-10 and TGF-.beta. have at least an additive effect in inducing alloantigen-specific tolerance, and that in vitro cytokines can be exploited to suppress CD4+ T cell-mediated Ag-specific responses in vivo.

L11 ANSWER 4 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)

96:620928 The Genuine Article (R) Number: VC450. THYMIC DEPENDENCE OF LOSS OF TOLERANCE IN MIXED ALLOGENEIC BONE-MARROW CHIMERAS AFTER DEPLETION OF DONOR ANTIGEN - PERIPHERAL MECHANISMS DO NOT CONTRIBUTE TO MAINTENANCE OF TOLERANCE. KHAN A; TOMITA Y; SYKES M (Reprint). HARVARD UNIV, MASSACHUSETTS GEN HOSP, TRANSPLANTAT BIOL RES CTR, SURG SERV, SCH MED, MGH-E, BOSTON, MA, 02129 (Reprint); HARVARD UNIV, MASSACHUSETTS GEN HOSP, TRANSPLANTAT BIOL RES CTR, SURG SERV, SCH MED, BOSTON, MA, 02129. TRANSPLANTATION (15 AUG 1996) Vol. 62, No. 3, pp. 380-387. ISSN: 0041-1337 . Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A nonmyeloablative conditioning regimen has recently been developed that allows allogeneic marrow engraftment with **induction** of permanent mixed chimerism and donor-specific tolerance across fully MHC-mismatched, allogeneic barriers, We recently demonstrated that tolerance can be broken in these chimeras by administration of an anti-donar class I-specific monoelonal antibody that eliminates donor hematopoietic cells, We have now investigated the role of the thymus ill the loss of tolerance observed when chimerism is eliminated in this manner, Mixed chimeras were prepared in B10 (H2(b)) recipients by treatment with depleting anti-CD4 and anti-CDS mAbs, 3-Gy whole body irradiation, and 7-Gy thymic irradiation, followed by B10.A (H2(a)) bone marrow transplantation. Chimeras were thymectomized 7 weeks later, and were either untreated or were depleted of donor cells with anti-donor class I (D-d-specific) mAb 34-2-12. Control chimeras that were not thymectomized also received anti-donor monoclonal antibodies or no further treatment, Of the four groups, only euthymic animals that were depleted of donor antigen showed a loss of tolerance, as evidenced by rejection of B10.A skin grafts. In contrast to untreated central and thymectomized, anti-Dd-treated chimeras, these euthymic anti-Dd-treated chimeras showed significant recovery of V beta 11(+) T cells, which can recognize Mtv antigens presented by donor I-E molecules, The requirement for a thymus for lass of tolerance in the absence of donor antigen was verified in an adoptive transfer model, in which chimera (B10.A-->B10) spleen cells were depleted of donor-type cells **ex vivo**, adoptively transferred into B6 nu/nu mice, and then further depleted of donor-type antigen with monoclonal antibody treatment in vivo. These B6 nu/nu mice maintained donor-specific tolerance to B10.A skin grafts. The absence of active suppression as a potent mechanism of tolerance in long-term mixed chimeras was confirmed by the loss of mixed chimerism and of tolerance that was readily induced by injection of naive host-type spleen cells. Together, our results suggest that in mixed allogeneic chimeras, intrathymic clonal deletion, and not peripheral suppression or anergy, is the major mechanism maintaining donor-specific tolerance.

L11 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1995:384152 Document No.: PREV199598398452. **Induction** of anergy in **ex vivo** alloreactive CD4 T cells by activated T cell expressing MHC class II. Satyaraj, E.; Rath, S.; Bal, V.. National Inst. Immunology, New Delhi 110 067 India. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 599. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:42:47 ON 12 FEB 2002

L1	3250	S T CELL TOLERANCE
L2	105	S L1 AND GRAFT REJECTION
L3	2	S L2 AND TGF BETA
L4	1	DUP REMOVE L3 (1 DUPLICATE REMOVED)
L5	23	S L1 AND EX VIVO
L6	11222831	S L5 AND INTERLEUKIN 2 OR 5
L7	11	DUP REMOVE L5 (12 DUPLICATES REMOVED)
L8	0	S L2 AND EX VIVO
L9	1521	S L1 AND INDUCTION
L10	8	S L9 AND EX VIVO

L11 5 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> s l9 and interleukin 15
L12 0 L9 AND INTERLEUKIN 15

=> s horwitz d?/au
L13 1277 HORWITZ D?/AU

=> s l13 and suppressor cell
3 FILES SEARCHED...
L14 40 L13 AND SUPPRESSOR CELL

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15 23 DUP REMOVE L14 (17 DUPLICATES REMOVED)

=> s l15 and IL2
L16 0 L15 AND IL2

=> s l15 and IL15
L17 0 L15 AND IL15

=> s l15 and TGF
L18 3 L15 AND TGF

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19 3 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-3 cbib abs

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
2001:763163 Document No. 135:302914 A method to prevent graft rejection using **TGF**-.beta. to induce T **suppressor cells** . **Horwitz, David** (University of Southern California, USA). PCT Int. Appl. WO 2001077299 A2 20011018, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US11898 20010411. PRIORITY: US 2000-PV196446 20000411.

AB The invention relates to compns. and methods useful for preventing graft rejection in a recipient following organ transplantation. Recipient CD4+ T cells are induced to become suppressor T cells in the presence of transforming growth factor-.beta. and donor cells. Other cytokines, such as interleukin 2 and interleukin 15, further comprise the compn. to increase the generation of **suppressor cells**.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
1999:626069 Document No. 131:256340 Use of cytokines and mitogens to inhibit graft versus host disease. **Horwitz, David A.** (University of Southern California, USA). PCT Int. Appl. WO 9948524 A1 19990930, 37 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US4630 19990303. PRIORITY: US 1998-PV76677 19980303.

AB Disclosed is a method for inducing T cell tolerance in a sample of ex vivo peripheral blood mononuclear cells, comprising the addn. to said cells of immunosuppressive agents such as IL-10 and **TGF**-.beta.. Also described is a kit for carrying out such a method and the relevance of the latter for instance for suppressing Graft Vs. Host Disease in patients that have received allogenic bone marrow transplants.

L19 ANSWER 3 OF 3 MEDLINE

95053723 Document Number: 95053723. PubMed ID: 7964469. The role of transforming growth factor beta in the generation of suppression: an interaction between CD8+ T and NK cells. Gray J D; Hirokawa M; **Horwitz D A**. (Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033.) JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Nov 1) 180 (5) 1937-42. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB CD8+ T cells have suppressor effector functions, but the mechanisms involved in the generation of this activity are poorly understood. We report that natural killer (NK) cells have an important role in the acquisition of this function. CD8+ cells induce NK cells to produce transforming growth factor-beta (**TGF**-beta) which, in turn, stimulates CD8+ T cells to become suppressors of antibody production. Using a monocyte-dependent and -independent method to induce antibody production, we first observed that the addition of NK cells to CD8+ cells was required for optimal suppression. Next, we determined that the interaction of CD8+ T cells with NK cells resulted in a striking increase NK cell **TGF**-beta mRNA and its production. This cytokine appeared to be involved in the induction of T **suppressor cell** activity since: (a) anti-**TGF**-beta 1 completely abrogated the suppression of immunoglobulin G synthesis; (b) **TGF**-beta 1 could substitute for NK cells in inducing CD8+ T cells to develop suppressor activity; and (c) a short exposure of T cells to **TGF**-beta 1 in the absence of B cells was sufficient for the generation of suppressor activity by CD8+ T cells. Interferon gamma did not have this property. These studies provide strong evidence that in addition to its suppressive properties, **TGF**-beta is involved in the generation of CD8+ T suppressor effector cells. Because NK cell function is decreased in many autoimmune diseases, these cells may fail to interact properly with these individuals' CD8+ cells in generating suppressors of aggressive anti-self responses.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:42:47 ON 12 FEB 2002

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L1          3250 S T CELL TOLERANCE
L2           105 S L1 AND GRAFT REJECTION
L3             2 S L2 AND TGF BETA
L4             1 DUP REMOVE L3 (1 DUPLICATE REMOVED)
L5            23 S L1 AND EX VIVO
L6      11222831 S L5 AND INTERLEUKIN 2 OR 5
L7            11 DUP REMOVE L5 (12 DUPLICATES REMOVED)
L8             0 S L2 AND EX VIVO
L9          1521 S L1 AND INDUCTION
L10            8 S L9 AND EX VIVO
L11            5 DUP REMOVE L10 (3 DUPLICATES REMOVED)
L12            0 S L9 AND INTERLEUKIN 15
L13         1277 S HORWITZ D?/AU
L14           40 S L13 AND SUPPRESSOR CELL
L15           23 DUP REMOVE L14 (17 DUPLICATES REMOVED)
L16            0 S L15 AND IL2
L17            0 S L15 AND IL15
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L18 3 S L15 AND TGF
L19 3 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l15 1-23 cbib abs

L15 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2002 ACS
2001:763163 Document No. 135:302914 A method to prevent graft rejection using TGF-.beta. to induce T **suppressor cells**. **Horwitz, David** (University of Southern California, USA). PCT Int. Appl. WO 2001077299 A2 20011018, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US11898 20010411. PRIORITY: US 2000-PV196446 20000411.

AB The invention relates to compns. and methods useful for preventing graft rejection in a recipient following organ transplantation. Recipient CD4+ T cells are induced to become suppressor T cells in the presence of transforming growth factor-.beta. and donor cells. Other cytokines, such as interleukin 2 and interleukin 15, further comprise the compn. to increase the generation of **suppressor cells**.

L15 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2002 ACS
2001:168120 Document No. 134:206587 Use of cytokines, cells, and mitogens to inhibit graft versus host disease. **Horwitz, David A.** (University of Southern California, USA). PCT Int. Appl. WO 2001016296 A2 20010308, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US40803 20000901. PRIORITY: US 1999-PV151987 19990901.

AB The field of the invention is generally related to pharmaceutical agents useful in treating graft-vs.-host disease in patients that have received allogenic bone marrow transplants. The invention provides methods for inducing T cell tolerance in a sample of ex vivo peripheral blood mononuclear cells comprising adding a suppressive-inducing compn. to the cells. The suppressive-inducing compn. can be interleukin-2, interleukin-10, transforming growth factor-.beta., or a mixt. The method also relates to a method whereby donor peripheral blood mononuclear cells are treated with a suppressive-inducing compn. to induce T-cell tolerance. The treated cells are then introduced into a recipient patient. T-cells can also be treated with transforming growth factor-.beta. and activated to become suppressor T-cells that inhibit graft vs. host disease.

L15 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2002 ACS
1999:626069 Document No. 131:256340 Use of cytokines and mitogens to inhibit graft versus host disease. **Horwitz, David A.** (University of Southern California, USA). PCT Int. Appl. WO 9948524 A1 19990930, 37 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US4630 19990303. PRIORITY: US 1998-PV76677 19980303.

AB Disclosed is a method for inducing T cell tolerance in a sample of ex vivo peripheral blood mononuclear cells, comprising the addn. to said cells of immunosuppressive agents such as IL-10 and TGF-.beta.. Also described is a kit for carrying out such a method and the relevance of the latter for instance for suppressing Graft Vs. Host Disease in patients that have received allogenic bone marrow transplants.

L15 ANSWER 4 OF 23 MEDLINE DUPLICATE 1
95053723 Document Number: 95053723. PubMed ID: 7964469. The role of transforming growth factor beta in the generation of suppression: an interaction between CD8+ T and NK cells. Gray J D; Hirokawa M; **Horwitz D A**. (Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033.) JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Nov 1) 180 (5) 1937-42. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.
AB CD8+ T cells have suppressor effector functions, but the mechanisms involved in the generation of this activity are poorly understood. We report that natural killer (NK) cells have an important role in the acquisition of this function. CD8+ cells induce NK cells to produce transforming growth factor-beta (TGF-beta) which, in turn, stimulates CD8+ T cells to become suppressors of antibody production. Using a monocyte-dependent and -independent method to induce antibody production, we first observed that the addition of NK cells to CD8+ cells was required for optimal suppression. Next, we determined that the interaction of CD8+ T cells with NK cells resulted in a striking increase NK cell TGF-beta mRNA and its production. This cytokine appeared to be involved in the induction of T **suppressor cell** activity since: (a) anti-TGF-beta 1 completely abrogated the suppression of immunoglobulin G synthesis; (b) TGF-beta 1 could substitute for NK cells in inducing CD8+ T cells to develop suppressor activity; and (c) a short exposure of T cells to TGF-beta 1 in the absence of B cells was sufficient for the generation of suppressor activity by CD8+ T cells. Interferon gamma did not have this property. These studies provide strong evidence that in addition to its suppressive properties, TGF-beta is involved in the generation of CD8+ T suppressor effector cells. Because NK cell function is decreased in many autoimmune diseases, these cells may fail to interact properly with these individuals' CD8+ cells in generating suppressors of aggressive anti-self responses.

L15 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1994:244074 Document No.: PREV199497257074. **Suppressor cells** generated by anti-CD2 block the induction of T cell-dependent B cell differentiation. Hirokawa, Makoto; Gray, J. Dixon; Wang, Hua; **Horwitz, David A.**. Div. Rheumatol., Dep. Med., Univ. Southern Calif. Sch. Med., Los Angeles, CA 90033 USA. FASEB Journal, (1994) Vol. 8, No. 4-5, pp. A1014. Meeting Info.: Experimental Biology 94, Parts I and II Anaheim, California, USA April 24-28, 1994 ISSN: 0892-6638. Language: English.

L15 ANSWER 6 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
94:190609 The Genuine Article (R) Number: ND197. **SUPPRESSOR CELLS** GENERATED BY ANTI-CD2 BLOCK THE INDUCTION OF T-CELL-DEPENDENT B-CELL DIFFERENTIATION. HIROKAWA M (Reprint); GRAY J D; WANG H; **HORWITZ D A**. UNIV SO CALIF, SCH MED, DEPT MED, LOS ANGELES, CA, 90033. FASEB JOURNAL (18 MAR 1994) Vol. 8, No. 5, pp. A1014. ISSN: 0892-6638. Pub country: USA. Language: ENGLISH.

L15 ANSWER 7 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1993:334227 Document No.: PREV199345028952. Parital characterization of a minor T cell subset in human peripheral blood that blocks antibody production induced by anti-CD2 monoclonal antibodies. Tsunoda, T.; Gray, J. D.; **Horwitz, D. A.**. Dep. Med., University Southern California, Sch. Med., Los Angeles, CA 90033 USA. Journal of Immunology, (1993) Vol. 150, No. 8 PART 2, pp. 192A. Meeting Info.: Joint Meeting of

the American Association of Immunologists and the Clinical Immunology Society Denver, Colorado, USA May 21-25, 1993 ISSN: 0022-1767. Language: English.

L15 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1993:175012 Document No.: PREV199344082612. Natural killer cells and systemic lupus erythematosus. Gray, J. Dixon; **Horwitz, David A.**. Univ. Southern Calif. Med. Sch., Los Angeles, CA USA. Wallace, D. J.; Hahn, B. H.. (1993) pp. 97-99. Dubois' lupus erythematosus, Fourth edition. Publisher: Lea and Febiger 200 Chesterfield Parkway, Malvern, Pennsylvania 19355, USA. ISBN: 0-8121-1494-9. Language: English.

L15 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1993:174782 Document No.: PREV199344082382. Systemic lupus erythematosus: Generalized autoimmunity arising from disordered immune regulation. **Horwitz, David A.**. Div. Immunol./Rheumatol., Sch. Med., Univ. South. Calif., Los Angeles, CA USA. McCarty, D. J.; Koopman, W. J.. (1993) pp. 2) 1185-1199. Arthritis and allied conditions: A textbook of rheumatology, Vols. 1 and 2, Twelfth edition. Publisher: Lea and Febiger 200 Chesterfield Parkway, Malvern, Pennsylvania 19355, USA. ISBN: 0-8121-1430-2. Language: English.

L15 ANSWER 10 OF 23 MEDLINE DUPLICATE 2
89036986 Document Number: 89036986. PubMed ID: 2972835. Further characterization of interleukin-2 production by lymphocytes of patients with systemic lupus erythematosus. Linker-Israeli M; Quismorio F P Jr; **Horwitz D A**. (Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033.) JOURNAL OF RHEUMATOLOGY, (1988 Aug) 15 (8) 1216-22. Journal code: JWX; 7501984. ISSN: 0315-162X. Pub. country: Canada. Language: English.
AB To further characterize the mechanisms responsible for defective interleukin-2 (IL-2) production in patients with systemic lupus erythematosus (SLE), we studied the effect of irradiation on the capacity of lymphocytes to produce this lymphokine when stimulated with phytohemagglutinin (PHA), or with a combination of PHA and a phorbol myristic acid ester (PMA). Irradiation increased PHA induced IL-2 production in patients with SLE and normal controls, and reached normal levels in 10 of 16 patients with SLE. This effect was due to inactivation of CD8+ **suppressor cells**. When PMA was used as a costimulant, maximal enhancement of IL-2 production was observed in both groups, but values in SLE remained significantly lower than in normals. These differences were not overcome by irradiation, raising the possibility that SLE **suppressor cells** act upon a site proximal to protein kinase C. Our studies have confirmed that active endogenous suppression may be responsible for most of the defective PHA induced IL-2 production in SLE and that this suppression is radiosensitive.

L15 ANSWER 11 OF 23 MEDLINE DUPLICATE 3
89029249 Document Number: 89029249. PubMed ID: 2972425. Characterization of lymphocytes that suppress IL-2 production in systemic lupus erythematosus. Linker-Israeli M; Gray J D; Quismorio F P Jr; **Horwitz D A**. (Department of Medicine, University of Southern California, School of Medicine, Los Angeles 910033.) CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1988 Aug) 73 (2) 236-41. Journal code: DD7; 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.
AB IL-2 production by peripheral blood mononuclear cells (PBM) is decreased in patients with systemic lupus erythematosus (SLE). This defect can be reversed by the removal of CD8+ lymphocytes. The purpose of these studies was to determine whether the CD8+ IL-2 **suppressor cells** comprise a specific subset or whether all CD8+ cells have this activity. Lymphocyte subsets were identified and separated by two-colour flow cytometry prior to a 48 h mitogen stimulation. The CD8+ cells that suppressed IL-2 production co-expressed HLA DR and were radiosensitive.

Other markers co-expressed by CD8+ cells which are found on **suppressor cells** such as Leu 15 (CD11), Leu 11 (CD16), and Leu 7 were also found on the CD8+ IL-2 **suppressor cell** population in SLE. In healthy subjects, removal of CD16+, but not of CD8+ cells markedly elevated the production of IL-2. The CD8- CD16+ non-T cell subset suppressed IL-2 production by normal and SLE PBM in autologous and allogeneic combinations. This subset may be a human equivalent of the murine natural **suppressor cells**. These results demonstrate that the cells that suppress IL-2 production in SLE are heterogeneous, and suggest that they belong to more than one lineage.

L15 ANSWER 12 OF 23 MEDLINE DUPLICATE 4
87102501 Document Number: 87102501. PubMed ID: 3492262. Characterization of immunologic function in homosexual men with persistent, generalized lymphadenopathy and acquired immune deficiency syndrome. Burkes R L; Abo W; Levine A M; Linker-Israeli M; Parker J W; Gill P S; Krailo M; **Horwitz D A**. CANCER, (1987 Feb 15) 59 (4) 731-8. Journal code: CLZ; 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB A syndrome of persistent, generalized lymphadenopathy (PGL), related to the acquired immune deficiency syndrome (AIDS), has been described in homosexual men. To further characterize and correlate the immunologic status of patients with PGL with those in AIDS, we studied spontaneous and pokeweed mitogen (PWM)-induced IgG synthesis by B-cells, T-cell subsets in peripheral blood (PB), natural cytotoxicity (NC), and Interleukins (IL)-1 and IL-2 production in 39 homosexual patients (21 PGL; 13 AIDS; five asymptomatic homosexual men), in whom 32 of 35 tested (91%) had antibodies to human T-lymphotropic virus-III (HTLV-III). A profound abnormality in B-cell function was found in AIDS and PGL, consisting of high spontaneous IgG production, with paradoxic suppression of IgG synthesis after PWM. IL-2 values were more often low in AIDS when compared with PGL (P less than 0.001). The PB lymphocyte count was normal in PGL and reduced in AIDS (P less than 0.001). OKT4 "helper" cells were decreased in PGL, but even lower in AIDS (P less than 0.001), while OKT8 "cytotoxic/ **suppressor" cells** were normal in AIDS and increased in PGL (P less than 0.01). The T4:T8 ratio was reversed in both, but more abnormal in AIDS (P less than 0.001). A decrease in NC killing was observed in AIDS when compared with heterosexual controls. Thus, patients with PGL and AIDS both demonstrate a spectrum of immunologic dysfunction, involving the cellular and humoral arms of the immune system.

L15 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1987:350715 Document No.: BR33:51336. SUPPRESSION OF SPONTANEOUS IGG PRODUCTION IN SYSTEM LUPUS ERYTHEMATOSUS BY AUTOLOGOUS CD8-POSITIVE LYMPHOCYTES TREATED WITH INTERLEUKIN 2. GRAY J D; LINKER-ISRAELL M; **HORWITZ D A**. USC SCH. MED., LOS ANGELES, CALIF.. SEVENTY-NINTH ANNUAL NATIONAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, SAN DIEGO, CALIFORNIA, USA, MAY 1-4, 1987. CLIN RES. (1987) 35 (3), 608A. CODEN: CLREAS. ISSN: 0009-9279. Language: English.

L15 ANSWER 14 OF 23 MEDLINE
87283622 Document Number: 87283622. PubMed ID: 2956420. Functional properties of CD8 positive lymphocyte subsets in systemic lupus erythematosus. **Horwitz D A**; Linker-Israeli M; Gray J D; Lemoine C. JOURNAL OF RHEUMATOLOGY, (1987 Jun) 14 Suppl 13 49-52. Journal code: JWX; 7501984. ISSN: 0315-162X. Pub. country: Canada. Language: English.

AB CD8+ lymphocytes comprise several cell subpopulations that differ phenotypically and functionally. Although the percentage of T cytotoxic/ **suppressor cells** (CD3+ CD8+) is usually increased in patients with active SLE, these lymphocytes are unable to suppress immunoglobulin (Ig) synthesis. However, freshly prepared lymphocytes from patients with SLE contain CD8+ DR+ cells which spontaneously suppress lymphocyte production of mitogen induced interleukin 2 (IL-2).

Furthermore, CD8+ Leu 11+ non-T cells which comprise only 5% of total lymphocytes are also potent suppressors of IL-2 production. At the present time it is not known whether CD8+ suppressors of Ig synthesis and CD8+ suppressors of IL-2 production represent different maturation stages of common precursor cells or represent true heterogeneity of CD8+ lymphocytes.

L15 ANSWER 15 OF 23 MEDLINE DUPLICATE 5
87009954 Document Number: 87009954. PubMed ID: 2944966. Suppressor T lymphocytes from lepromatous leprosy skin lesions. Modlin R L; Mehra V; Wong L; Fujimiya Y; Chang W C; **Horwitz D A**; Bloom B R; Rea T H; Pattengale P K. JOURNAL OF IMMUNOLOGY, (1986 Nov 1) 137 (9) 2831-4. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The immune response in leprosy forms a spectrum with lepromatous leprosy patients exhibiting specific unresponsiveness to antigens of Mycobacterium leprae. This unresponsiveness is thought to be related to the prevalence of T8-positive lymphocyte in these lepromatous lesions. To analyze the immunoregulatory function of these T8 cells, we developed simple procedures to extract lymphocytes from skin biopsy specimens of patients with leprosy. These lymphocytes were sorted for T8 and T4 positive cells, and cell lines were established by expansion with interleukin 2 (IL 2) and irradiated feeder cells. All T8 positive lines tested were positive for IL 2 receptors and HLA-DR determinants. These lines were additionally assayed for lepromin-induced suppression of the normal peripheral blood lymphocyte Con A proliferative response. Thirteen of 32 lines from six lepromatous patients showed significant suppressor activity, whereas nine lines from six tuberculoid patients and one line from normal peripheral blood failed to show suppression (p less than 0.001). Taken together, the finding of M. leprae-triggered **suppressor cells** within lepromatous skin lesions may in part explain the M. leprae unresponsiveness of lepromatous leprosy patients.

L15 ANSWER 16 OF 23 MEDLINE DUPLICATE 6
85131787 Document Number: 85131787. PubMed ID: 3156152. Correction of interleukin-2 production in patients with systemic lupus erythematosus by removal of spontaneously activated **suppressor cells**. Linker-Israeli M; Bakke A C; Quismorio F P Jr; **Horwitz D A**. JOURNAL OF CLINICAL INVESTIGATION, (1985 Feb) 75 (2) 762-8. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Interleukin-2 (IL-2) production in vitro is depressed in systemic lupus erythematosus (SLE) patients. It is not known whether this abnormality is caused by a defect in the producer lymphocytes or by excessive suppression. We report that removal of OKT8 (Leu 2a)+ cells increased the IL-2 production by in vitro-stimulated lymphocytes to normal or above normal levels in 19 of 21 SLE patients. This increase was more apparent in those patients with clinically inactive disease and/or receiving less than 7.5 mg of prednisone. Removal of OKT8+ cells from normals did not significantly increase IL-2 activity. SLE, but not normal, OKT8+ cells decreased IL-2 production when added back to autologous OKT8-depleted cells. In some experiments, OKT8+ cells from normal donors also suppressed IL-2 production in SLE. This result suggests that the defect in IL-2 production is complex and may involve multiple cell interactions. Three lines of evidence suggest that the SLE OKT8+ cells actively inhibit the production of IL-2 rather than passively absorb this lymphokine: (a) only 3.2% of SLE lymphocytes expressed IL-2 receptors as detected with anti-Tac; (b) freshly prepared SLE lymphocytes did not absorb IL-2; and (c) cell-free supernatants from SLE OKT8+ cells inhibited IL-2 production, but not IL-2 activity. Double-labeling studies by flow cytometry revealed that 19.3% of SLE OKT8+ cells were also Ia-positive, and approximately 33% co-expressed the natural killer cell marker, HNK-1 (Leu 7). Removal of Leu 7+ cells also significantly elevated IL-2 production in SLE. These studies suggest that one or more circulating mononuclear cell subsets in SLE

patients can suppress IL-2 production and that one subset may possibly belong to a non-T, non-B "third mononuclear population."

L15 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1985:180475 Document No.: BR29:70471. DELINEATION OF A LEU-2 T-8-POSITIVE LEU-15-NEGATIVE LEPROMIN-SPECIFIC T **SUPPRESSOR CELL** SUBSET IN LEPROMATOUS LEPROSY. MODLIN R L; REA T; WONG L; UDIS B; **HORWITZ D A**. USC SCH. MED., LOS ANGELES, CALIF. 90033.. 42ND ANNUAL NATIONAL MEETING OF THE AMERICAN FEDERATION FOR CLINICAL RESEARCH, WASHINGTON, D.C., USA, MAY 3-6, 1985. CLIN RES. (1985) 33 (2 PART 1), 383A. CODEN: CLREAS. ISSN: 0009-9279. Language: English.

L15 ANSWER 18 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
85:228582 The Genuine Article (R) Number: AEY93. DELINEATION OF A LEU-2 (T8)&, LEU 15-LEPROMIN-SPECIFIC T-**SUPPRESSOR CELL** SUBSET IN LEPROMATOUS LEPROSY. MODLIN R L (Reprint); REA T; WONG L; UDIS B; **HORWITZ D A**. UNIV SO CALIF, SCH MED, LOS ANGELES, CA, 90033. CLINICAL RESEARCH (1985) Vol. 33, No. 2, pp. A383. Pub. country: USA. Language: ENGLISH.

L15 ANSWER 19 OF 23 MEDLINE DUPLICATE 7
83230874 Document Number: 83230874. PubMed ID: 6602614. T lymphocyte subsets in systemic lupus erythematosus. Correlations with corticosteroid therapy and disease activity. Bakke A C; Kirkland P A; Kitridou R C; Quismorio F P Jr; Rea T; Ehresmann G R; **Horwitz D A**. ARTHRITIS AND RHEUMATISM, (1983 Jun) 26 (6) 745-50. Journal code: 90M; 0370605. ISSN: 0004-3591. Pub. country: United States. Language: English.
AB The contribution of immune regulation to the etiology of systemic lupus erythematosus (SLE) is poorly understood. Using the monoclonal antibodies OKT4 and OKT8, we quantitated, by flow cytometry, T inducer/helper and T cytotoxic/**suppressor cells** in patients with SLE. Serologically active patients, who had clinical manifestations such as arthritis or rash and were not receiving prednisone, were characteristically lymphopenic due to a marked reduction in OKT4+ cells. Prednisone therapy produced the same phenomenon. Untreated patients, who were serologically inactive, demonstrated no abnormalities. These studies have thus revealed two presumably independent factors that can produce similar immunoregulatory aberrations.

L15 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1983:2496 Document No.: BR24:2496. T CELL SUBSETS IN PROGRESSIVE SYSTEMIC SCLEROSIS. EHRESMANN G R; **HORWITZ D A**; BAKKE A C. UNIV. SOUTHERN CALIF. SCH. MED., LOS ANGELES, CALIF. 90033.. 8TH PAN-AMERICAN CONGRESS OF RHEUMATOLOGY IN CONJUNCTION WITH THE ANNUAL SCIENTIFIC MEETINGS OF THE AMERICAN RHEUMATISM ASSOCIATION AND THE ARTHRITIS HEALTH PROFESSIONS ASSOCIATION, WASHINGTON, D.C., USA, JUNE 7-12, 1982. ARTHRITIS RHEUM. (1982) 25 (4 SUPPL), S45. CODEN: ARHEAW. ISSN: 0004-3591. Language: English.

L15 ANSWER 21 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
81211312 EMBASE Document No.: 1981211312. Regulation of antigen-induced lymphoproliferation by BSA gradient-separated T cell fractions. Emmons R.P.; Carvalho E.M.; **Horwitz D.A.**. Rheumatol. Div., Dept. Int. Med., Univ. Virginia, Charlottesville, VA 22908, United States. Journal of Immunology 127/3 (821-824) 1981.
CODEN: JOIMA3. Pub. Country: United States. Language: English.
AB Human T cells from 6 volunteers immunized with key-hole limpet hemocyanin (KLH) or tetanus toxoid were fractionated on bovine serum albumin (BSA) gradients. These T cell fractions were then recombined with autologous unseparated mononuclear cells or unseparated T cells to determine the effect of each fraction on the proliferative (DNA synthetic) response to the immunizing antigen. Using this separation technique, we were able to define 2 fractions of T cells of widely different densities that had a suppressive effect on the proliferative response to KLH of unfractionated

T cells. The demonstration of suppressive activity was possible only if cells were tested within 8 wk of immunization with KLH. These suppressive T cell fractions differed not only in density but also in surface characteristics. Fraction 1 cells had a high proportion of Ia+ cells but no Fc receptors for IgG (FcR(G)-) were seen, whereas cells from fraction 4 (of higher density) were Ia- and were composed of 12.1 .+-. 1.2% FcR(G)+ cells. This suppression was shown to be specific for the immunizing antigen. One individual who had been immunized with KLH for more than 1 yr in which suppression of KLH-induced proliferation was no longer demonstrable was given primary immunization to tetanus toxoid. Suppression could be demonstrated in fractions 1 and 4 specific for tetanus toxoid; there was no demonstrable effect of these T cell fractions on the response to KLH. We postulate that these are different functional populations of suppressor T cells that regulate antigen specific lymphoproliferation.

L15 ANSWER 22 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
80099770 EMBASE Document No.: 1980099770. Methyldopa inhibition of suppressor-lymphocyte function. A proposed cause of autoimmune hemolytic anemia. Kirtland III H.H.; Mohler D.N.; **Horwitz D.A.**. Dept. Int. Med., Univ. Virginia Med. Cent., Charlottesville, Va. 22908, United States. New England Journal of Medicine 302/15 (825-832) 1980. CODEN: NEJMAG. Pub. Country: United States. Language: English.

AB To test the hypothesis that methyldopa induces red-cell autoantibodies by inhibiting the activity of suppressor lymphocytes, we studied its effect on several immune functions. Methyldopa inhibited T-lymphocyte suppression of IgG production by peripheral-blood mononuclear cells stimulated by pokeweed mitogens. This effect occurred in isolated T cells incubated with methyldopa and in T cells obtained from patients taking methyldopa. In addition, the drug caused a 30 to 80 per cent reduction in the proliferative response of peripheral-blood mononuclear cells to mitogens in vitro, and this reduction primarily involved the activation of T lymphocytes. Methyldopa also caused a persistent elevation of intracellular lymphocyte cyclic AMP in vitro and in vivo. We postulate that methyldopa alters the immune system by causing a persistent increase in lymphocyte cyclic AMP, which inhibits suppressor T-cell function. These effects may lead to unregulated autoantibody production by B cells in some patients.

L15 ANSWER 23 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
80148321 EMBASE Document No.: 1980148321. Conditions required for Fc-dependent immune complex enhancement of antigen-specific lymphocyte blastogenesis. Carvalho E.M.; Davis IV J.S.; **Horwitz D.A.**. Div. Rheumatol., Dept. Int. Med., Univ. Virginia Sch. Med., Charlottesville, Va. 22908, United States. Journal of Immunology 124/2 (565-570) 1980. CODEN: JOIMA3. Pub. Country: United States. Language: English.

AB The conditions required for enhancement of antigen-specific lymphocyte proliferation by immune complexes were investigated in this study. Healthy volunteers were immunized with keyhole limpet hemocyanin (KLH). Lymphocytes from these donors and nonsensitized controls were stimulated with either KLH alone or KLH-IgG anti-KLH immune complexes, and blastogenesis was measured by incorporation of 3H-thymidine measured after 3 to 6 days of incubation. Neither uncomplexed Ag nor immune complexes stimulated lymphocytes from unimmunized donors. Immune complexes significantly enhanced KLH-specific lymphocyte blastogenesis of lymphocytes from immunized donors under certain conditions. When concentrations of KLH one-tenth to one-half that required for the optimal response were complexed with IgG antibody, these immune complexes elicited a blastogenic response that was 2- to 4-fold greater than that induced by antigen alone. In contrast, IgG antibody complexed to the optimal stimulatory concentration (125 .mu.g/ml) had no enhancing effects. Kinetic studies revealed that immune complexes stimulated lymphocytes to proliferate 36 hr earlier than comparable cultures containing antigen alone. Enhancement was greatest in days 3 to 5 of culture and was no longer apparent by day 6. The Fc portion of the antibody molecule was

required for enhanced DNA synthesis because enhancement was not observed when immune complexes were prepared with F(ab')2 fragments of anti-KLH antibodies or when cell suspensions were depleted of lymphocytes with Fc receptors capable of binding these complexes. These experiments suggest that immune complexes containng small quantities of antigen may, through a Fc-bearing lymphocyte intermediate, stimulate helper T cells. This enhancement of Ag-specific proliferation disappears with complexes containing greater quantities of antigen possibly by activation of **suppressor cells**.

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